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| 10/067,624 | 02/04/2002 | Roberto Valducci | 242/9-1646 | 4252 |

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| EXAMINER | |
|---|---|
| PAK, JOHN D | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1616 | |

DATE MAILED: 08/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/067,624 | VALDUCCI, ROBERTO | |
| | Examiner | Art Unit | |
| | JOHN D PAK | 1616 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *03 May 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *10-18 and 20-28* is/are pending in the application.

4a) Of the above claim(s) *10-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Claims 1-9 have been canceled. Claims 10-18 and 20-28 are pending in this application. Claims 10-18 remain withdrawn from further consideration as being directed to non-elected subject matter. Claims 20-28 will presently be examined.

This Office action is in reply to applicant's amendments and remarks of 5/3/2004. Applicant's amendments and remarks indicate that the amended claimed invention is directed to a multiparticulate formulation comprising microgranules or micro-tablets, which formulation is not a monolithic formulation, that is to say, the claimed formulation is not pressed or otherwise further processed to produce a monolithic tablet or monolithic capsule[1]. Previously, such a feature was not seen to be mandatory since there was no requirement that the multiparticulate formulation could not be further processed. With the maximum size of microgranules or micro-tablets being so large (2 mm), and in the absence of contrary indication, the claims were previously reasonably readable on monolithic tablets made from multiparticulates or multiple counts of 2mm tablets. However, in view of applicant's amendments and remarks, the claims will presently be interpreted somewhat differently, as requiring multiple particulates.

Applicant is advised of a misspelling in claim 25, line 2: "metacrylic" should be corrected to --- methacrylic --- (emphasis added).

[1] See applicant's remarks on page 6, third full paragraph, of the reply filed on 5/3/2004.

In the previous Office action, the amendment filed on 10/10/2003 was objected to under 35 USC 132 and previously pending claim 7 was rejected under 35 USC 112, first paragraph. The objection and rejection are withdrawn because it can now be recognized that, even though myriad EUDRAGIT® products are known, the originally disclosed EUDRAGIT L, RS, RL, L 30 D and NE 30 D, taken with the Degussa product information of record, which was provided by applicant, provide adequate descriptive support for the amendment to the specification and claims.

The following is a quotation of the first paragraph of 35 USC 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 21 is rejected under 35 USC 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Dependent claim 21 reads on lithium salt content of up to 1000 mg/g. This means the formulation contains 100 percent by weight lithium salt. This is impossible because the independent claim 20 requires additional ingredients such as a coating.

Since the coating will take up some weight percentage, maximum of 100 percent lithium salt is impossible. The claim is plainly not enabled.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in – (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United states before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for the purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 20, 23, 24, 26 are rejected under 35 USC 102(b) as being anticipated by Gai et al. for the disclosure of which was fully stated in the previous Office action (1/27/04 mail date, pages 6-9). In sum, lithium carbonate at 300 mg (68.5 wt%) + HPMC (Methocel K4MP) at 120 mg, Eudragit S 100 at 15.5 mg are combined to form a coated granule (p. 133, left and right columns, see all of the subsection, "Formulations"). 18 mesh sizing means maximum size is about 1 mm or 1000 μm.

Clearly, Gai et al. explicitly disclose multiple granules with a size below 1000 μm that contain lithium carbonate, HPMC and Eudragit S 100. Since Eudragit products are copolymers of acrylic and methacrylic acid, all features of above-noted claims are necessarily disclosed by Gai et al. and the claims are anticipated.

Applicant may argue that Gai et al. further compress the multiparticulate granules to tablets, thereby forming a monolithic form, i.e. not a multiparticulate form. However, it is the Examiner's position that Gai et al. clearly and expressly still disclose multiparticulate granules that read on applicant's claims. The fact that Gai et al. disclosed such granules means that the claims are anticipated. The fact that Gai et al. further processed the granules does not militate against finding anticipation because the granules were in separate and permanent existence prior to being compressed – they were dried for 2 hours (see sentence bridging the two columns on p. 133). Since applicant's claims read on Gai's granules, the claims cannot be avoid being found anticipated just because applicant found a different use for them, i.e. to fill them in capsules instead of compressing them. For these reasons, the claims are anticipated.

Claims 20, 22-24, 26 are rejected under 35 U.S.C. 102(e) as being anticipated by Tarro (US 2004/0013746).

Tarro explicitly discloses a "Once-a-Day" controlled release formulation of lithium carbonate to ensure a constant plasma concentration over 24 hours (lines 1-5 of paragraph 0003). The composition is in the form of coated granulates, which contain 93 wt% lithium carbonate, 1.7 wt% ethylcellulose, 0.8 wt% talc, 4.5 wt% polyvinylpyrrolidone (lines 6-9 of paragraph 0003; see also claims 1-3). Final granule size is between 840 μm and 1340 μm (paragraph 0028). Sample 1 as disclosed on

page 1 shows the following in vitro dissolution profile:

1 hour – 9.1%

4 hours – 38.7%

8 hours – 59.4%

12 hours – 69.8%

24 hours – 90%.

The claims are thereby anticipated.

It is noted that applicant claims the benefit of an earlier filed Italian application. However, the claim of priority has not been perfected because a certified translation of said Italian application has not bee filed.

Claims 20, 24, 26-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Paradissis et al. (EP 396425).

Paradissis et al. explicitly disclose an extended release pharmaceutical formulation that is capable of approaching zero order release of a drug over a "12 to at least 24 hour period" (p. 3, lines 40-41; p. 6, lines 15-23; claim 32). Lithium carbonate is exemplified as a suitable pharmaceutical ingredient to prepare as particles (p. 5, lines 1-2 & 16). A drug such as lithium carbonate may be present in amounts up to about 85 wt% (p. 5, lines 29-31). The formulation is composed of a mixture of the following components (p. 3, lines 42-46; p. 6, lines 10-14; p. 7, lines 18-30):

0-50 wt% of an immediate release particle, the size of which is -10+60 mesh; and

> Up to 100 wt% of an extended release particle comprising the particle coated with a dissolution modifying system containing plasticizers and a film forming agent, wherein the particle size of the extended release particle is -10+60 mesh[2].

Suitable film forming agents include acrylic and methacrylic acid copolymers and cellulose derivatives such as ethylcellulose and hydroxypropylmethylcellulose (p. 6, lines 42-47; see also claims 1, 5-6, 8 claims 6 and 8 in particular).

The claims are thereby anticipated. The only claim feature that requires further discussion is that of dependent claim 27. There, the formulation requires "uncoated microgranules" as well as coated microgranules. The Examiner shall interpret "uncoated" to encompass microgranules that do not have an extended release coating since it is not possible for a granule to not have some coating of at least impurities.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 28 is rejected under 35 U.S.C. 103(a) as being unpatentable over Paradissis et al. (EP 396425).

Teachings of Paradissis et al. have already been discussed earlier in this Office action, and the discussion there is incorporated herein by reference to avoid repetition.

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[2] The -10+60 mesh disclosure means that the particles pass through 10 mesh but not through 60 mesh. This would give a particle size range of approximately 250 μm to 2000 μm.

Further, it is noted again that Paradissis' disclosure is for a formulation that approaches "zero order release of drug over a 12 to at least 24 hour period" (page 3, lines 40-41). Range of dissolution of an exemplified potassium chloride formulation shows 1 hour dissolution rage of 0-50%, 8 hour dissolution range of 20-70% and 24 hour dissolution range of not less than 60% (p. 13, lines 26-45).

The difference between the claimed invention and the cited reference is that the reference does not expressly disclose the exact dissolution profile of applicant's claim 28. However, the cited reference does disclose a formulation approaching zero order release and various other examples of dissolution profiles that are within such dissolution profile. Given that a zero order release for a 24 hour period would necessarily provide approximately the rate of dissolution claimed in applicant's claim 28, taken with the guidance provided by another inorganic salt active ingredient formulation (KCl), one having ordinary skill in this art would have been motivated to provide an extended release coating that would approximate a zero order dissolution profile for lithium carbonate that would be well within the dissolution profile claimed herein.

Therefore, the claimed invention, as a whole, would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, because every element of the invention and the claimed invention as a whole have been fairly suggested by the cited reference.

Claim 25 is rejected under 35 U.S.C. 103(a) as being unpatentable over Paradissis et al. (EP 396425) in view of Gai et al., Rafiee-Tehrani et al. and Degussa product information (submitted by applicant on 10/10/2003 as prior art).

Teachings of Paradissis et al. have already been discussed earlier in this Office action, and the discussion there is incorporated herein by reference to avoid repetition. Further, it is noted again that Paradissis teaches lithium carbonate as the drug to be delivered and acrylic acid and methacrylic acid copolymers as the film forming agent in the extended release, dissolution modifying system (p. 6, lines 28-47, line 44 in particular).

The difference between Paradissis et al. the invention of claim 25 is that Paradissis et al. do not expressly disclose any specific copolymers of acrylic acid and methacrylic acid such as those recited in claim 25. However, Gai et al. suggest the use of Eudragit S 100 for formulating lithium carbonate (see p. 133, left column). Rafiee-Tehrani et al. also suggest the use of various Eudragit products such as Eudragit L 100, S 100, RL 100 and RS 100 to form "retardant barriers" for lithium carbonate controlled release (see page 87, left column, last paragraph of section 1 and section 2.1; see also page 88,m right column, wherein particles larger than 35 μm were coated with such polymers). Further, Degussa product information discloses a family of Eudragit products which are all acrylic and methacrylic acid copolymers. Therefore, given Paradissis' teaching to formulate lithium carbonate in a zero order, 24 hour extended release formulation with film forming agents such as acrylic and methacrylic acid copolymers, use of various Eudragit products such as those claimed in instant claim 25

are fairly suggested. The motivation to use one of the specifically claimed acrylic and methacrylic copolymers arises from the known benefit of acrylic and methacrylic acid copolymers for formulating lithium carbonate from Paradissis' teachings as well as Gai's and Rafiee-Tehrani's teachings and ready commercial availability of Eudragit products, as evidenced by Degussa's product information.

Therefore, the claimed invention, as a whole, would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, because every element of the invention and the claimed invention as a whole have been fairly disclosed or suggested by the teachings of the cited references.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

A facsimile center has been established in Technology Center 1600. The hours of operation are Monday through Friday, 8:45 AM to 4:45 PM. The telecopier number for accessing the facsimile machines is (703) 872-9306.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Examiner John Pak whose telephone number is **(571)272-0620.** The Examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's SPE, Gary Kunz, can be reached on **(571)272-0887**.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number **is (571) 272-1600**.

JOHN PAK
PRIMARY EXAMINER
GROUP 1600